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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission: 9

Application Number	09/716,842
Filing Date	November 17, 2000
First Named Inventor	BRIESEWITZ, ROGER
Group Art Unit	1644
Examiner Name	Huyhn, P.
Attorney Docket Number	STAN-131

ENCLOSURES (check all that apply)

- ☒ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment / Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☒ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Documents
- ☐ Response to Missing Parts/ Incomplete Application
  - ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Assignment Papers *(for an Application)*
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
- ☐ After Allowance Communication to Group
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to Group *(Appeal Notice, Brief, Reply Brief)*
- ☐ Proprietary Information
- ☐ Status Letter
- ☒ Other Enclosure(s) *(please identify below):*

  Response to Paper No. 11

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual Name	BRET E. FIELD, Reg. No. 37,620
Signature	
Date	January 10, 2002

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FEE TRANSMITTAL for FY 2002

Patent fees are subject to annual revision.

TOTAL AMOUNT OF PAYMENT	**($) 110.00**

Complete if Known	
Application Number	09/716,842
Filing Date	November 17, 2000
First Named Inventor	BRIESEWITZ, ROGER
Examiner Name	Huynh, P.
Group Art Unit	1644
Attorney Docket No.	STAN-131

METHOD OF PAYMENT

1. ☒ The Commissioner is hereby authorized to charge indicated fees and credit overpayments to:
   Deposit Account Number **50-0815**
   Deposit Account Name **Bozicevic, Field & Francis LLP**
   ☒ Charge Any Additional Fee Required Under 37 CFR 1.1 6 and 1.17
   ☐ Applicant Claims small entity status. **See 37 CFR 1.27**

2. ☐ **Payment Enclosed:**
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FEE CALCULATION

2. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
101	740	201	370	Utility filing fee	
106	330	206	165	Design filing fee	
107	510	207	255	Plant filing fee	
108	740	208	370	Reissue filing fee	
114	160	214	80	Provisional filing fee	
				SUBTOTAL (1)	

1. EXTRA CLAIM FEES

		Extra Claims		Fee from below	Fee Paid
Total Claims	24 -20**	=	x		=
Indep. Claims	5-3**	=	x		=
Multiple Dependent					=

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
103	18	203	9	Claims in excess of 20
102	84	202	42	Independent claims in excess of 3
104	280	204	140	Multiple dependent claim, if not paid
109	84	209	42	** Reissue independent claims over original patent
110	18	210	9	** Reissue claims in excess of 20 **and over original patent**

SUBTOTAL (2) $

***or number previously paid, if greater; For Reissues, see above.*

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge – late filing fee or oath	
127	50	227	25	Surcharge – late provisional filing fee or cover sheet	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for *ex parte* reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examination action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	110.00
116	400	216	200	Extension for reply within second month	
117	920	217	460	Extension for reply within third month	
118	1,440	218	720	Extension for reply within fourth month	
128	1,960	228	980	Extension for reply within fifth month	
119	320	219	160	Notice of Appeal	
120	320	220	160	Filing a brief in support of an appeal	
121	280	221	140	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive – unavoidable	
141	1,280	241	640	Petition to revive – unintentional	
142	1,280	242	640	Utility issue fee (or reissue)	
143	460	243	230	Design issue fee	
144	620	244	310	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Processing fee under 37 CFR 1.17(q)	
126	180	126	180	Submission of Information Disclosure Stmt	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	740	246	370	For each additional invention to be examined (37 CFR § 1.129(a))	
149	740	249	370	For each additional invention to be examined (37 CFR § 1.129(b))	
179	740	279	370	Request for Continued Examination (RCE)	
169	900	169	900	Request for expedited examination of a design application	

Other fee (specify)_____

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($)

SUBMITTED BY

				Complete (*if applicable*)	
Name (Print/Type)	**Bret E. Field**	*Registration No. (Attorney/Agent)*	**37,620**	*Telephone*	**(650) 327-3400**
Signature				*Date*	**01/10/2002**

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09/719,465
FA0975
Associate Power of Attorney
Petition for Extension of Time
Fee Transmittal for FY 2002
Amendment - 10 pages
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Signature	Teri Muir	**Date**	JAN. 10, 2002

REPONSE TO PAPER NO. 11 Address to: Assistant Commissioner for Patents Washington, D.C. 20231	Attorney Docket Confirmation No.	STAN-131
	First Named Inventor	Crabtree
	Application Number	09/716,842
	Filing Date	November 17, 2000
	Group Art Unit	1644
	Examiner Name	P. Huynh
	Title	TARGETED BIFUNCTIONAL MOLECULES AND THERAPIES BASED THEREON

#

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2-13-02

Dear Sir:

This communication is responsive to the Office Action dated September 25, 2001.

REMARKS

In view of the following remarks, the Examiner is respectfully requested to withdraw the rejections and allow Claims 16-36, the only claims pending and currently under examination in this application.

Prior to addressing the issues in the office action, it is believed that a brief review of the invention is helpful. The invention is directed to methods of modifying the biodistribution of an administered drug by administering the drug as a bifunctional molecule, where the drug is conjugated to a ligand that binds to a structure, e.g., protein, present in the host to which the drug is administered. For example, by administering the drug as a conjugate with a ligand of an intracellular protein, the subject invention provides for modified biodistribution of the drug such that it located preferentially in intracellular spaces. Likewise, by administering the drug as a conjugate with a ligand of an extracellular protein, the subject invention provides for modified

biodistribution of the drug such that it locates preferentially in extracellular spaces. The present invention is based on the ingenious manner in which the inventors have satisfied this need for a small molecule biodistribution modulator, i.e. by administering the drug itself as, a small, i.e., less than 5000 dalton, bifunctional molecule that includes a ligand that binds to the biodistribution modulating structure .

Turning now to the rejections presented in the Office Action, Claims 16-36 were rejected under 35 U.S.C. §102 (b) as being anticipated by WO 95/10302 published application.

With respect to anticipation, it is well established that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ 2d 1051, 1053 (Fed. Cir. 1987), *cert. denied*, 481 U.S. 1052 (1987). *See also, Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 USPQ 2d 1001 (Fed. Cir. 1991).

The present claims are directed to methods of modulating the biodistribution of a drug by administering the drug as bifunctional molecule, in which the drug is present as a conjugate with a ligand for an intracellular or extracellular structure, where this ligand is referred to in the claims as a targeting moiety. In other words, **the drug is part of the bifunctional molecule**.

A careful reading of the WO 95/10302 published application shows that this document does not, in fact, teach administration of a drug as a conjugate with another ligand for the purpose of modulating the biodistribution of the drug, which is what is claimed in Claims 16-36 and is a critical element of these claims. In other words, this application does not teach a method in which the distribution of a drug is modified by administering the drug as a bifunctional molecule.

Applicants acknowledge that this application does disclose approaches for modifying the distribution of drugs or toxins present in the blood stream of an individual by administering bifunctional molecules to the individual. However, the bifunctional molecules do not include the drug whose distribution is to be modified as part of the molecule. Specifically, the conjugates

disclosed by the WO 95/10302 published application are conjugates of a first binding member and a second binding member, where the second binding member binds to a long-lived blood component and the first binding member is a target binding member, which binds to a variety of different targets, including a drug. See the abstract of this published application.

For example, this publication discloses a bifunctional molecule that is a conjugate of two antibody moieties, one of which binds to cocaine and one of which binds to a red blood cell. The purpose of this bifunctional molecule is to immobilize cocaine molecules on the surface of red blood cells to modify the distribution of the cocaine drug molecules. See e.g., Example 1. While the distribution of the drug molecule, i.e., cocaine, is modified with the disclosed bifunctional molecules, it is modified by an entirely different mechanism from that which is claimed in the pending claims of the present application. In the mechanism of the WO 95/10302 publication, the drug is administered by itself and then bound by the bifunctional molecule, which does not include the drug itself, but instead includes a drug binding moiety, i.e., an antibody that specifically binds to cocaine, conjugated to a long-lived blood component binding moiety.

In contrast, the claimed methods of the present application modify the biodistribution of a drug by administering the drug itself as a bifunctional molecule with a second ligand (targeting moiety) that binds to a structure which will modify the biodistribution of the drug. As such, the claimed methods are completely different from those disclosed in the WO 95/10302 publication, since the drug itself is present in the administered bifunctional molecule, and the bifunctional molecule does not just include a ligand that binds to the drug, which is what is disclosed in the WO 95/10302 publication.

In view of the above remarks, it is apparent that the WO 95/10302 publication does not disclose a method in which the biodistribution of a drug is modulated by administering the drug itself as a bifunctional molecule. Since administration of the drug itself as a bifunctional molecule is a claimed element of the pending claims, and this element is not disclosed in WO 95/10302, the WO 95/10302 fails to anticipate the claimed methods, as it fails to disclose each element of the claimed methods.

Furthermore, with respect to Claims 19, 24-26 and 36, these claims are specifically directed to targeting a drug to an intracellular space, since the ligand component of the bifunctional molecule is limited to a ligand for an intracellular protein.

In contrast, the WO 95/10302 published application is explicitly directed only to methods of maintaining a drug in an extracellular space. Throughout the disclosure of the WO 95/10302 application, the target binding member is a member that binds to a long-lived blood component. As such, the WO 95/10302 published application does not teach or even suggest a bifunctional molecule in which the ligand component of the molecule binds to an intracellular protein.

Because the WO 95/10302 published application fails to teach or event suggest a bifunctional molecule in which the ligand component of the molecule binds to an intracellular protein, it clearly does not anticipate Claims 19, 24-26 and 36, which claims include the limitation that the ligand bind to an intracellular protein.

As such, WO 95/10302 fails to anticipate Claims 16-36 under 35 U.S.C. §102 (b) and this rejection may be withdrawn.

Claims 16-36 were also rejected under 35 U.S.C. §102 (e) as being anticipated by U.S. Patent No. 5,843,440. This patent contains the same disclosure as the above discussed WO 95/10302 application. As such, for the reasons provided above, Claims 16-36 are not anticipated under 35 U.S.C. §102 (e) by U.S. Patent No. 5,843,440 and this rejection may be withdrawn.

Finally, the Examiner has rejected Claims 16-36 under 35 U.S.C. § 103(a) as being obvious over either WO 95/10302 or U.S. Patent No. 5,843,440 in view of U.S. Patent No. 5,830,462, asserting that the only difference between the claimed methods and the primary references is the size of the bifunctional molecules, which element is made up by the `462 patent.

However, as pointed out above, the primary references are fundamentally different from the claimed methods in that, when they disclose methods of modifying the distribution of drug, they teach mechanisms in which the distribution of the drug is modified by administering a

bifunctional molecule of a ligand for the drug and a ligand for long-lived blood component. **They do not teach or suggest administering the drug itself as a bifunctional molecule.**

The cited supplemental 5,830,462 patent does not make up the above deficiency in the primary references. The `462 patent discloses bifunctional molecules that cause homodimerization or heterodimerization of two structures, e.g., chimeric proteins, that are present in an environment, e.g., a cell. Contrary to the Examiner's characterization of this disclosure on page 6 of the office action, no teaching in this patent can be found as to where this patent discloses modifying the biodistribution of a drug by administering it as a bifunctional molecule. Where targeting to different locations is desired, the only teaching that can be found in this patent is in the section titled "Exocytosis" beginning at the bottom of Column 14. However, in this section of the patent, the location of chimeric proteins is modified by bifunctional molecule mediated oligomerization of the chimeric proteins. The biodistribution of a drug is not modified by administering it as a bifunctional molecule. (If indeed the 462 patent does teach biodistribution of a drug as stated in the second full paragraph of page 6 of the office action, the Examiner is requested to provide more specific support for this statement.)

Because the `462 patent fails to teach modulation of biodistribution of drug by administering it as a bifunctional molecule and the Examiner has only cited this patent for its teaching of small sized bifunctional molecules, this reference fails to make up the fundamental deficiencies in the primary references as discussed above. Accordingly, the combined teachings of the WO 95/10302 or 5,843,440 references in view of the 5,830,462 reference fails to teach or suggest the claimed methods.

Because the combined teachings of the WO 95/10302 or 5,843,440 references in view of the 5,830,462 reference fails to teach or suggest the claimed methods, Claims 16 to 36 are not obvious under 35 U.S.C. § 103 over these references and this rejection may be withdrawn.

In view of the above remarks, this application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issuance.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815.

Respectfully submitted,

BOZICEVIC, FIELD & FRANCIS LLP

Date: 1·10·02

By: _____
Bret E. Field
Registration No. 37,620

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